DATA EVALUATION RECORD

DICAMBA BAPMA SALT

STUDY TYPE: SUBCHRONIC 90-DAY ORAL TOXICITY STUDY – RAT
OCSPP 870.3100; OECD 408

MRID 49441801

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202

Prepared by
Summitec Corporation
9724 Kingston Pike, Suite 602
Knoxville, Tennessee 37922

Task Order No. 6-118

Primary Reviewer: Jennifer Rayner, Ph.D., D.A.B.T.	Signature: Date:	Jennifer Rayner 12/01/2014
Secondary Reviewers: Thomas C. Marshall, Ph.D., D.A.B.T.	Signature: Date:	Thomas C. Marshall 12/01/2014
Robert H. Ross, M.S., Program Manager	Signature: Date:	Robert H. Ross 12/01/2014
Quality Assurance: Angela M. Edmonds, B.S.	Signature: Date:	Angela M. Edmonds 12/01/2014

Disclaimer
This review may have been altered subsequent to the contractor's signatures above.

EPA Reviewer: William Irwin, PhD, DABT **Signature:** _____
Health Effects Division (7509P) **Date:** _____
EPA Secondary Reviewer: Linda Taylor, PhD **Signature:** _____
Health Effects Division (7509P) **Date:** _____

Template version 09/11

TXR#:

DATA EVALUATION RECORD

STUDY TYPE: 90-Day Oral Toxicity Dietary Study - Rat;
OCSPP 870.3100 [§82-1a] (rodent); OECD 408.

PC CODE: 100094 **DP BARCODE:**

TEST MATERIAL (PURITY): Dicamba BAPMA Salt (69.5% Dicamba acid)

SYNONYMS: BAS 183 22H

CITATION: Flick, B., V. Strauss, H. Marxfeld, *et al.* (2014). Dicamba BAPMA Salt repeated dose 90-day oral toxicity study in Wistar rats administration via the diet. BASF SE (Ludwigshafen, Germany). Laboratory project number 50C0519/13C071, July 4, 2014. MRID 49441801. Unpublished.

SPONSOR: BASF SE, 67056 Ludwigshafen, Germany.

EXECUTIVE SUMMARY:

In a 90-day oral toxicity study (MRID 49441801), Dicamba BAPMA Salt (69.5% a.i. Dicamba acid; batch#: 1781-6) was administered to 10 Wistar rats/sex/dose in the diet at dose levels of 0, 4317, 8633, or 17266 ppm (equivalent to 0, 257, 513, and 1027 mg/kg bw/day in males and 0, 294, 589, and 1178 mg/kg bw/day in females). The test diets were equivalent to 0, 3000, 6000, and 12000 ppm Dicamba acid (equivalent to 0, 178, 357, and 714 mg/kg bw/day in males and 0, 205, 409, and 819 mg/kg bw/day in females). Evaluated parameters included mortality, clinical signs, body weight, food consumption, ophthalmological examinations, functional observational battery (FOB), clinical pathology, organ weight, and gross and histopathological examination.

There were no treatment-related effects on mortality, clinical signs, FOB, body weights, food consumption, ophthalmoscopy, urine parameters, macroscopic findings, or histopathology. Treatment-related increased absolute and relative kidney weights were noted in males of the high-dose study group (absolute weight 15% greater than controls [n.s.] and relative weight 20% greater than controls). Total bilibrubin levels were significantly decreased 41-79% in all treated animals, and the changes were considered related to treatment, but were not considered adverse. In males of the high-dose group, prolonged prothrombin time (9.5%) and increased incidence of urine triple phosphate crystals were observed. In females, creatinine levels were significantly increased 33% at the high-dose. In both sexes at the high-dose, total protein and globulin levels were significantly decreased 5-16%. **Therefore, under the conditions of this study, the LOAEL of Dicamba BAPMA Salt is 17266 ppm (1027 mg/kg bw/day in males and 1178**

mg/kg/day in females; corresponding to 714 and 819 mg/kg bw/day Dicamba Acid in males and females, respectively), based on kidney effects and altered hematology (increased prothrombin time in males) and clinical chemistry (increased creatinine levels in females and decreased total protein and globulin levels in both sexes) parameters. The NOAEL is 8633 ppm (513 mg/kg bw/day in males and 589 mg/kg/day in females; corresponding to 357 and 409 mg/kg bw/day Dicamba Acid in males and females, respectively).

This 90-day oral toxicity study in the rat is **Acceptable / Guideline** and satisfies the guideline requirement for a 90-day oral toxicity study (OCSPP 870.3100; OECD 408).

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS:

A. MATERIALS:

1. Test material: Dicamba BAPMA Salt

Description: White to yellowish solid
Lot/batch #: 1781-6
Purity: 84.7% w/w, equiv. to 69.5% a.i. Dicamba acid
Compound stability: Stability under storage conditions guaranteed by sponsor; stored at room temperature protected against humidity and temperatures <5°C and > 30°C
CAS # of TGAI: Not available
Structure: Not available

2. Vehicle and/or positive control: Ground Kliba maintenance diet mouse/rat "GLP" meal

3. Test animals:

Species: Rat
Strain: Crl:WI(Han)
Age/weight at study initiation: Age: 42±1 day; Weight: Males: 142.6-186.8 g; Female: 115.1-149.4 g
Source: Charles River Laboratories, Sulzfeld, Germany
Housing: Housed 5/cage in H-Temp polysulfonate cages with a floor area of ~2065 cm^2 and dust-free wooden bedding. Wooden gnawing blocks and large play tunnels were supplied for environmental enrichment. Motor activity measurements were conducted in polycarbonate cages having a floor area of ~800 cm^2.
Diet: Ground Kliba maintenance diet mouse/rat"GLP" meal *ad libitum*
Water: Drinking water *ad libitum*
Environmental conditions:
Temperature: 20-24°C
Humidity: 30-70%
Air changes: 15/hr
Photoperiod: 12 hrs dark/12 hrs light
Acclimation period: 8 days

B. STUDY DESIGN:

1. In life dates: Start: January 7, 2014; End: April 23, 2014

2. Animal assignment: Animals were randomly assigned to the test groups noted in Table 1. The animals were distributed according to weight with variations not exceeding 20% of the mean weight of each sex.

TABLE 1: Study design [a]

Test group	# Animals	Dicamba BAPMA Salt conc. in diet (ppm)	Dicamba BAPMA Salt dose to animal (mg/kg bw/day)[b]		Dicamba acid conc. in diet (ppm)	Dicamba acid dose to animal (mg/kg bw/day)[b]	
			Male	Female		Male	Female
Control	10/sex	0	0	0	0	0	0
Low	10/sex	4317	257	294	3000	178	205
Mid	10/sex	8633	513	589	6000	357	409
High	10/sex	17266	1027	1178	12000	714	819

[a] Data taken from p. 24 and 51, MRID 49441801.
[b] Calculated using the 95% lower confidence limit

3. **Dose selection rationale:** The dose levels were selected based on request of the sponsor.

4. **Diet preparation and analysis:** Diet was prepared by mixing appropriate amounts of premix (test substance mixed with small amount of food) with Ground Kliba maintenance diet mouse/rat "GLP" meal and was stored at room temperature. The frequency of test diet preparation was not reported. The stability of test substance in the diet at 1250 ppm was tested for 32 days at room temperature. Homogeneity and concentration were tested in samples of treated food at all dose levels five times during the study.

Results:
Homogeneity analysis: The relative standard deviations were ranged from 2% to 8.6% and were less than ≤10% and were acceptable.

Stability analysis: The test substance was stable in Ground Kliba maintenance diet mouse/rat "GLP" meal for over 32 days at room temperature. Concentrations were in the range of 90-110% of nominal.

Concentration analysis: No test substance was detected in the control samples. Of the 40 samples analyzed, most (Samples 7-33 and 38-40) were within 90-110% of nominal concentration. Samples 34-36 were within ±15% of the target concentration and were considered acceptable. Samples 3-6, low- and mid-dose, were below the specification limit (70-84%) and the test diet preparation method was changed to avoid replication of the problem. The analytical data indicated that the mixing procedure was adequate after the first five days of dosing and that the variance between nominal and actual dosage to the animals was acceptable. It is not expected that the overall study was affected by the short deviation in test diet concentrations.

5. **Statistics:** Body weight and body weight changes were analyzed by Dunnett's test. FOB, blood, and urine parameters and organ weights were analyzed by Kruskal-Wallis test and Wilcoxon test. Statistical significance was set at $p \leq 0.05$ and $p \leq 0.01$. The reviewer considers the statistical analyses appropriate.

C. **METHODS:**

1. **Observations:**

1a. **Cageside observations:** Animals were inspected twice daily for signs of toxicity and mortality and weekdays and once daily on weekends and holidays.

1b. **Clinical examinations:** Detailed clinical examinations were conducted prior to test initiation and weekly in a standard arena. The following parameters were examined: abnormal behavior, fur, skin, posture, salivation, respiration, activity/arousal level, tremors, convulsions, abnormal movements, gait abnormalities, lacrimation, palpebral closure, exophthalmos, feces and urine discharge, and pupil size.

1c. **Neurological evaluations:** The FOB was performed in all animals at the end of the study. The methods, environmental conditions, duration of observations, strain gauges, and scoring criteria were adequately described. It was not reported that the observers

were blind to the animals' group assignment. No positive control data were submitted. The CHECKED (X) parameters were examined:

	HOME CAGE OBSERVATIONS		HANDLING OBSERVATIONS		OPEN FIELD OBSERVATIONS
X	Posture		Reactivity	X	Rearing count
	Biting	X	Lacrimation/ chromodacryorrhea		Arousal/ general activity level
X	Convulsions	X	Salivation	X	Convulsions
X	Tremors		Piloerection	X	Tremors
X	Abnormal Movements	X	Fur appearance	X	Abnormal movements
	Palpebral closure	X	Palpebral closure	X	Urination / defecation
	Feces consistency		Eye prominence		Grooming
X	Gait abnormalities	X	Respiration characterization	X	Gait abnormalities / posture
X	Reaction to removal		Red/crusty deposits*	X	Bizarre / stereotypic behavior
	SENSORY OBSERVATIONS	X	Mucus membranes /eye /skin color		Backing
					Time to first step
	Visual reaction		Muscle tone	X	Posture
X	Touch response		Extensor thrust		
X	Auditory response				
X	Pain (tail pinch) response		**PHYSIOLOGICAL OBSERVATIONS**		
X	Visual placing response				
X	Air righting reflex		Body weight		
X	Pupil size and response		Body temperature		**NEUROMUSCULAR OBSERVATIONS**
X	Startle response				
	Eyeblink response				Hindlimb extensor strength
	Forelimb extension		**OTHER OBSERVATIONS**	X	Forelimb grip strength
	Hindlimb extension	X	Motor activity	X	Hindlimb grip strength
	Olfactory orientation			X	Landing foot splay
X	Approach response				Rotarod performance
X	Pinna reflex				

2. **Body weight:** Animals were weighed prior to study initiation and weekly thereafter.

3. **Food consumption and compound intake:** Food consumption for each animal was determined weekly and calculated as mean food consumption in grams per animal and day. Compound intake (mg/kg bw/day) values were calculated from the consumption and body weight gain data.

4. **Ophthalmoscopic examination:** Eyes were examined in all animals at the beginning and at the end of the study in animals of the control and high-dose group.

5. **Hematology and clinical chemistry:** Blood was collected from the retro-bulbar venous plexus of fasted animals for hematology and clinical chemistry. The CHECKED (X) parameters were examined.

a. Hematology:

X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)*
X	Leukocyte count (WBC)*	X	Mean corpusc. HGB conc.(MCHC)*
X	Erythrocyte count (RBC)*	X	Mean corpusc. volume (MCV)*
X	Platelet count*	X	Reticulocyte count
	Blood clotting measurements*		
	(Thromboplastin time)		
	(Clotting time)		
X	(Prothrombin time)		

* Recommended for 90-day oral rodent studies based on Guideline 870.3100

b. Clinical chemistry:

X	ELECTROLYTES	X	OTHER
X	Calcium	X	Albumin*
X	Chloride	X	Creatinine*
	Magnesium	X	Urea nitrogen*
X	Phosphorus	X	Total Cholesterol*
X	Potassium*	X	Globulins
X	Sodium*	X	Glucose*
	ENZYMES (more than 2 hepatic enzymes eg., *)	X	Total bilirubin
X	Alkaline phosphatase (ALP)*	X	Total protein (TP)*
	Cholinesterase (ChE)	X	Triglycerides
	Creatine phosphokinase		Serum protein electrophoresis
	Lactic acid dehydrogenase (LDH)		
X	Alanine aminotransferase (ALT/also SGPT)*		
X	Aspartate aminotransferase (AST/also SGOT)*		
	Sorbitol dehydrogenase*		
X	Gamma glutamyl transferase (GGT)*		
	Glutamate dehydrogenase		

* Recommended for 90-day oral rodent studies based on Guideline 870.3100

6. **Urinalysis*:** Urine was collected from fasted animals overnight in metabolism cages prior to necropsy. The CHECKED (X) parameters were examined.

X	Appearance*	X	Glucose
X	Volume*	X	Ketones
X	Specific gravity/osmolality*	X	Bilirubin
X	pH*	X	Blood/blood cells*
X	Sediment (microscopic)		Nitrate
X	Protein*	X	Urobilinogen

* Optional for 90-day oral rodent studies

7. **Sacrifice and pathology**: All animals that died and those sacrificed on schedule were subjected to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. Tissues from animals in the control and high-dose group were examined histologically. All gross lesions were examined in all groups. The (XX) organs, in addition, were weighed in all animals.

X	DIGESTIVE SYSTEM
	Tongue
X	Salivary glands*
X	Esophagus*
X	Stomach*
X	Duodenum*
X	Jejunum*
X	Ileum*
X	Cecum*
X	Colon*
X	Rectum*
XX	Liver*+
	Gall bladder (not rat)*
	Bile duct (rat)
X	Pancreas*
X	**RESPIRATORY**
X	Trachea*
X	Lung*
X	Nose*
X	Pharynx*
X	Larynx*

X	CARDIOVASC./HEMAT.
X	Aorta*
XX	Heart*+
X	Bone marrow*
X	Lymph nodes*
XX	Spleen*+
XX	Thymus*+
X	**UROGENITAL**
XX	Kidneys*+
X	Urinary bladder*
XX	Testes*+
XX	Epididymides*+
X	Prostate*
X	Seminal vesicles*
XX	Ovaries*+
XX	Uterus*+
X	Mammary gland*
X	Oviducts
X	Vagina

X	NEUROLOGIC
XX	Brain*+
X	Peripheral nerve*
X	Spinal cord (3 levels)*
X	Pituitary*
X	Eyes (optic nerve)*
X	**GLANDULAR**
XX	Adrenal gland*+
X	Lacrimal gland
X	Parathyroid*
XX	Thyroid*
X	**OTHER**
X	Bone (sternum and/or femur)
X	Skeletal muscle
X	Skin*
X	All gross lesions and masses*

* Recommended for 90-day oral rodent studies based on Guideline 870.3100
+ Organ weights required for rodent studies.

II. RESULTS:

A. OBSERVATIONS:

1. **Clinical signs of toxicity:** There were no treatment-related effects observed.

2. **Mortality:** There were no mortalities during the study.

3. **Neurological evaluations:** There were no treatment-related effects on home cage evaluations, open field evaluations, sensorimotor tests/reflexes, or quantitative parameters. In motor activity tests (Table 2), interval numbers 1 and 2 were significantly increased at 8633 and 17266 ppm, and intervals 1-12 were significantly increased at 4317 and 8633 ppm in males. In females at 4317 ppm, only the first interval of motor activity was significantly increased. The changes in motor activity were not considered to be treatment-related because of the lack of dose response.

TABLE 2. Mean motor activity [a]

Dose rate (ppm)	Motor activity (mean±SD, n=10)					
	Interval 1	Interval 2	Interval 6	Interval 9	Interval 12	Intervals 1-12
Male						
0	652.9±100.8	467.3±96.9	42.3±54.3	15.0±23.3	14.2±18.1	1800.9±305.6
4317	676.6±118.1	496.2±110.2	85.9±114.8	49.4±75.1	37.5±40.0	2171.5±387.2* (20.6)
8633	944.5±332.7* (44.7)[b]	722.0±93.0** (54.5)	105.9±123.0	30.1±36.3	9.3±13.4	2708.5±830.5** (50.4)
17266	805.6±157.9* (23.4)	594.2±154.2* (27.2)	10.6±9.6	18.9±21.8	35.0±64.7	2073.8±388.1
Female						
0	836.5±244.6	495.8±116.8	79.7±119.4	35.8±53.9	24.8±27.7	2296.9±673.2
4317	1135.6±269.1* (35.8)	662.1±241.6	30.6±40.8	57.7±57.5	36.9±77.9	2676.7±637.0
8633	839.2±181.4	557.9±203.3	38.0±56.6	43.3±38.1	14.3±16.9	2142.5±784.1
17266	861.8±168.4	579.8±137.2	56.9±118.6	122.6±158.8	80.9±131.9	2503.7±883.3

[a] Data obtained from Tables IA43—IA46, pp. 110-113, MRID 49441801.
[b] Numbers in parentheses equal percent change, relative to control value.
* Statistically different ($p < 0.05$) from the control.
** Statistically different ($p < 0.01$) from the control.

B. <u>BODY WEIGHT AND WEIGHT GAIN</u>: Body weight and body weight gain data are shown in Table 3. There were no treatment-related effects on body weight in males, but body weight gains at the high-dose were significantly ($p<0.05$) decreased 25%, relative to control, during the first week of the study. In females of the mid-dose group, body weights were significantly ($p<0.05$) increased 8% and 9% on study days 56 and 70, respectively, and cumulative body weight gains were significantly increased ($p<0.05$) 14% and 16% from days 0-56 and 0-70, respectively.

TABLE 3. Average body weights and body weight gains during 90 days of treatment [a]						
Dose rate (ppm)	Body weights (g±SD, n=10)				Total weight gain	
	Day 0	Week 1	Week 7	Week 13	g	Relative to control (%)
Male						
0	161.0±12.1	200.5±15.6	334.3±35.7	386.0±42.2	225.0±37.3	-
4317	162.7±11.3	204.7±13.8	350.7±24.7	400.8±28.6	238.2±21.7	5.9
8633	163.3±13.8	201.8±16.6	331.9±36.2	376.0±43.4	212.6±33.5	-5.5
17266	162.9±12.0	192.4±15.7	320±37.1	370.5±46.2	207.6±37.3	-7.7
Female						
0	129.3±8.9	149.2±9.2	214.3±11.6	231.0±18.9	101.7±15.6	-
4317	131.8±5.7	150.5±8.5	216.8±12.6	239.6±15.9	107.8±13.5	6.0
8633	133.7±8.8	153.0±10.9	229.2±18.6	251.3±20.7	117.6±15.6	15.7
17266	129.9±7.0	145.7±11.8	213.6±16.5	235.5±20.0	105.5±14.8	3.8

[a] Data obtained from Tables IA9-IA20, pp. 76-87, MRID 49441801.
* Statistically different ($p < 0.05$) from the control.
** Statistically different ($p < 0.01$) from the control.

C. FOOD CONSUMPTION AND COMPOUND INTAKE:

1. **Food consumption:** No treatment-related changes were observed. An unusually high amount of food spillage at 8633 and 17266 ppm prevented calculation of mean food consumption values. It was noted that the body weights were not different among the groups.

2. **Compound consumption:** Test substance intake of the salt and corresponding acid is shown in Table 1. The authors noted that calculations of test substance intake based on estimated food consumption would be biased and result in high exposure levels due to the large amount of food spillage. The high exposure levels would be more than twice the target exposure. Therefore, the authors estimated food consumption leading to a lower test substance intake in the range of the target exposure levels, which was a more conservative approach. Due to the lack of significantly decreased body weights and body weight gains, it was assumed that the animals ate the normal amount of diet to sustain growth comparable to the concurrent controls. The authors assumed a worst case scenario and used the 95% lower confidence interval limit of their historical control data to calculate test substance intake. The approach was more likely to underestimate food consumption and test substance intake which would link adverse effects to a lower exposure level. Effects were interpreted using the lower exposure levels.

D. OPHTHALMOSCOPIC EXAMINATION: There were no treatment-related effects.

E. BLOOD ANALYSES:

1. **Hematology:** Selected hematology data are shown in Table 4a. In males, prothrombin time was significantly prolonged at the high-dose. The authors suggested that dysregulation of the coagulation system possibly due to reduced synthesis of coagulation factors in the liver. Large unstained cell counts were significantly lower in all treated groups of males compared to controls. No patho-physical findings were associated with the decreased large unstained

cell counts, so the changes were regarded as incidental. There were no treatment-related effects in females.

TABLE 4a. Selected hematology data [ab]

Observation	Dose (ppm)			
	0	4317	8633	17266
Males				
Prothrombin time (s)	37.0±2.4	36.2±2.9 (-2.2)	38.2±1.3 (3.2)	40.5±1.5** (9.5)[c]
Large unstained cell counts (%)	0.7±0.4	0.4±0.2* (-42.9)	0.4±0.2* (-42.9)	0.3±0.1** (-57.1)
Females				
Prothrombin time (s)	34.3±2.7	34.8±0.8	34.6±1.5	35.5±1.5
Large unstained cell counts (%)	0.5±0.2	0.4±0.3	0.5±0.2	0.5±0.1

[a] Data obtained from Tables IB1-IB4, pp 116-119

[a] Data obtained from Tables IB1-IB4, pp. 116-119, MRID 49441801.
[b] Values are given as Mean ± Standard Deviation, n=10 for all groups.
[c] Numbers in parentheses equal percent change, relative to control value.
* Statistically different ($p < 0.05$) from the control.
** Statistically different ($p < 0.01$) from the control.

2. **Clinical chemistry:** Selected clinical chemistry data are shown in Table 4b. Alkaline phosphatase activity was significantly decreased in males of the low-dose group and significantly increased in males of the high-dose group. The effect in the low-dose group was considered to be incidental. In the high-dose group, the effect was considered to be treatment-related and may be correlated with the significantly increased relative liver weight observed in the males. Globulin levels were significantly decreased in males at the mid-dose, but the values were within the historical control range. In females, creatinine levels were significantly increased at the mid- and high-doses and were considered to be treatment-related. Total protein and globulin levels were significantly decreased in both sexes in the high-dose groups. Total bilirubin levels were significantly decreased in all treated animals. The study authors suggested that liver enzyme induction resulted in increased conjugation rate of bilirubin leading to an accelerated excretion of bilirubin via the bile. The effects were regarded as treatment-related but not adverse. There was a dose-related decrease in cholesterol in males, although statistical significance was not attained and females did not show a similar effect. Additionally, a non-statistically significant increase in triglycerides levels was observed in the high-dose females only.

TABLE 4b. Selected clinical chemistry data [ab]

Observation	Dose (ppm)			
	0	4317	8633	17266
Males				
Alkaline phosphatase (µkat/L)	1.28±0.14	1.15±0.13* (-10.2)[c]	1.29±0.28 (0.8)	1.52±0.21** (18.8)
Total bilirubin (µmol/L)	1.44±0.17	0.85±0.16** (-41.0)	0.58±0.22** (-59.7)	0.34±0.11** (-76.4)
Total protein (g/L)	64.52±2.88	63.27±2.40 (-1.9)	62.25±1.66 (-3.5)	59.76±1.63** (-7.4)
Globulin (g/L)	25.34±2.11	24.50±1.57 (-3.3)	23.26±1.14* (-8.2)	21.32±1.07** (-15.9)
Cholesterol (mmol/L)	1.95±0.47	1.88±0.32	1.61±0.25 (-17.4)	1.54±0.25 (-21.0)
Females				
Creatinine (µmol/L)	30.7±2.9	31.9±3.9 (3.9)	34.3±2.9* (11.7)	40.9±5.4** (33.2)
Total bilirubin (µmol/L)	1.95±0.39	1.13±0.33** (-42.1)	0.62±0.16** (-68.2)	0.41±0.19** (-79.0)
Total protein (g/L)	67.55±2.84	67.39±2.48 (-0.2)	65.47±1.85 (-3.1)	64.12±1.94* (-5.1)

TABLE 4b. Selected clinical chemistry data [ab]				
Observation	Dose (ppm)			
	0	4317	8633	17266
Globulin (g/L)	24.87±1.00	24.88±1.20 (0)	23.95±1.64 (-3.7)	22.88±1.26** (-8.0)
Triglycerides (mmol/L)	0.48±0.15	0.39±0.12	0.44±0.17	0.61±0.16 (+27.0)

[a] Data obtained from Tables IB5-IB8, pp. 120-123, MRID 49441801.
[b] Values are given as Mean ± Standard Deviation, n=10 for all groups.
[c] Numbers in parentheses equal percent change, relative to control value.
* Statistically different ($p < 0.05$) from the control.
** Statistically different ($p < 0.01$) from the control.

F. URINALYSIS: Urine pH values were significantly decreased in males of the low- and mid-dose groups and increased in females of the high-dose group. A significant increase in the number of triple phosphate crystals was observed in males of the high-dose group, but no association was found between urine crystals and increased relative kidney weights.

G. SACRIFICE AND PATHOLOGY:

1. **Organ weight:** Selected organ weights are shown in Table 5. The absolute weight of adrenal glands in males of the high-dose group was significantly decreased and outside of the historical control range. The relative adrenal weights were significantly decreased in females of the high-dose group, but were within the historical control range. There were no associated histopathological findings, and the differences in adrenal weights were not considered related to treatment. Relative ovary weights in females of the high-dose group were significantly decreased, but were within the historical control range. Relative liver weights in males of the high-dose group were significantly increased, compared to control, but the values were within the historical control range, and not considered related to treatment.

   Absolute kidney weights in the males of the high-dose group were increased 15%, but the increase was not statistically significant compared to controls. Relative kidney weights were significantly increased and both were regarded as treatment-related effects because both were outside of the historical control range.

[a] Data obtained from Tables IC1-IC13, pp. 130-137, MRID 49441801.

TABLE 5. Selected organ weight data [ab]				
Observation	Dose (ppm)			
	0	4317	8633	17266
Males				
Terminal body wt (g)	359.34±39.127	376.82±26.336 (4.9)	352.08±39.888 (-2.0)	346.91±43.886 (-3.5)
Absolute adrenal wt (mg)	65.4±8.959	61.9±7.549 (-5.1)	57.0±9.357 (-12.8)	53.7±6.816** (-17.9)
Organ/body ratio (%)	0.018±0.002	0.016±0.002 (-11.1)	0.016±0.003 (-11.1)	0.016±0.002 (-11.1)
Absolute kidney wt (g)	2.303±0.332	2.451±0.211 (6.4)	2.337±0.305 (1.5)	2.65±0.522 (15.1)
Organ/body ratio (%)	0.64±0.046	0.651±0.047 (1.7)	0.663±0.028 (3.6)	0.766±0.131** (19.7)
Absolute liver wt (g)	7.914±1.232	8.286±0.923 (4.5)	7.633±1.203 (-3.6)	8.257±1.193 (4.3)
Organ/body ratio (%)	2.196±0.15	2.195±0.124 (0)	2.163±0.159 (-1.5)	2.377±0.107** (8.2)
Females				
Terminal body wt (g)	215.95±14.957	222.66±15.017 (3.1)	235.2±20.295 (8.9)	220.17±16.933 (2.0)
Absolute adrenal wt (g)	73.3±7.689	76.7±9.707 (4.6)	72.8±7.495 (-0.7)	66.2±9.138 (-9.7)
Organ/body ratio (%)	0.034±0.004	0.035±0.005 (2.9)	0.031±0.002* (-8.8)	0.030±0.002** (-11.8)
Absolute ovary wt (mg)	102.9±11.03	101.1±9.085 (-1.1)	99.0±8.705 (-3.1)	89.9±14.918 (-12.0)
Organ/body ratio (%)	0.048±0.005	0.045±0.004 (-6.3)	0.042±0.005* (-12.5)	0.041±0.005** (-14.6)

[b] Values are given as Mean ± Standard Deviation, n=10.
[c] Numbers in parentheses equal percent change, relative to control value.
* Statistically different ($p < 0.05$) from the control.
** Statistically different ($p < 0.01$) from the control

2. **Gross pathology:** There were no treatment-related findings.

3. **Microscopic pathology:** There were no treatment-related findings.

III. DISCUSSION AND CONCLUSIONS:

A. INVESTIGATORS' CONCLUSIONS:

Treatment-related clinical pathology findings, prolonged prothrombin time and decreased globulin and total protein, were observed at the highest dose tested. Therefore, the no-observed-effect-level (NOAEL) for both sexes was 8633 ppm.

B. REVIEWER COMMENTS:

The Agency agrees with the NOAEL value. There were no treatment-related effects on mortality, clinical signs, FOB, body weights, food consumption, ophthalmoscopy, urine parameters, macroscopic findings, or histopathology. Treatment-related increased absolute and relative kidney weights were noted in males of the high-dose study group. Total bilibrubin levels were significantly decreased in all treated animals, and were considered related to treatment, but were not considered adverse. In males of the high-dose group, prolonged prothrombin time (3.5 seconds) and increased incidence of urine triple phosphate crystals were observed. In females, creatinine levels were significantly increased at the high-dose. In both sexes at the high-dose, total protein and globulin levels were significantly decreased.

Therefore, under the conditions of this study, the LOAEL of Dicamba BAPMA Salt is 17266 ppm (1027 mg/kg bw/day in males and 1178 mg/kg/day in females; corresponding to 714 and 819 mg/kg bw/day Dicamba Acid in males and females,

respectively), based on kidney effects and altered hematology (increased prothrombin time in males) and clinical chemistry (increased creatinine levels in females and decreased total protein and globulin levels in both sexes) parameters. The NOAEL is 8633 ppm (513 mg/kg bw/day in males and 589 mg/kg/day in females; corresponding to 357 and 409 mg/kg bw/day Dicamba Acid in males and females, respectively).

The reviewer notes that effects on the liver were observed, but were not attributed to treatment. Relative liver weights were significantly increased 8.5% in males at the high-dose but were within historical control range and less than 10% different from control. Alkaline phosphatase was significantly increased 18.8% in males of the high-dose group and total bilirubin was significantly decreased 76-79% in males and females of the high-dose group. It may be that, given time or higher dose levels, these effects may have been attributed to treatment with the test substance, but as dose levels were close to the limit dose of 1000 mg/kg bw/day, the effects may be purely incidental.

C. **STUDY DEFICIENCIES:** No deficiencies were noted.